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Research Article

EFFECT OF SUPERDISINTEGRANTS ON FORMULATION OF TASTE MASKED FAST DISINTIGRATING LISINOPRIL TABLETS

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ABSTRACT

The present investigation deals with the formulation of taste masked fast disintegrating tablets of Lisinopril that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy. Lisinopril is a drug that is primarily used in the treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complication of diabetes that acts by inhibiting angiotension convertingenzyme(ACE). The influence of superdisintegrants, crosspovidone, croscaremellose sodium on disintegration time, wetting time and water absorption ratio were studied. Tablets were evaluated for weight and thickness variation, disintegration time, drug content, *in vitro* dissolution, wetting time and water absorption ratio. The *in vitro* disintegration time of the best fast disintegrating tablets was found to be with in 32 seconds. Tablets containing crospovidone exhibit quick disintegration time than tablets containing croscaremellose sodium. The fast disintegrating tablets of Lisinopril with shorter disintegration time, acceptable taste and sufficient hardness could be prepared using crospovidone and other excipients at optimum concentration.

Keywords: Crosspovidone, Fast disintegrating tablet, Lisinopril, Superdisintigrants, Wetting time.

INTRODUCTION

Orally administered dosages form e.g. tablets, capsules are convenient dosage form for many drugs but they are challenging to formulate if the active substances has poor dissolution or low bioavailability. Polymer coating enables the formulation of mouth dissolving and taste masking of bitter taste drugs-thereby giving better patient compliance[1]. Most pharmaceutical forms for oral administration are formulated for direct ingestion, for chewing, for prior dispersion and /or dissolution in water; some of them are absorbed in mouth (sublingual or buccal tablets). Elderly individuals have difficulty in swallowing when prescribed in conventional tablet and capsule form [2, 3, 4]. The problem of swallowing is also evident in pediatrics, psychiatric as well as traveling patients who may not have ready access to water[5].The rapidly disintegrating tablet in mouth or orodispersible tablets overcome all the above problems and thus offer an alternate form of oral medication, which provide patients with a more convenient means of taking their medication [6].Cyclodextrin is the most widely used complexing agent for inclusion complex formation which is capable of masking the bitter taste of drug either by decreasing its solubility in digestin or by trapping the drug with in its cyclic structure long enough to retard initial dissolution and so decreasing the amount of drug particles exposed to taste buds there by reducing its precipitation of bitter taste. Addition of super disintegrating agent in the formulation is one of the approaches to formulate orodispersible tablets.Orally disintegrating tablets contain wide variety of pharmaceutical active ingredients covering many therapeutic categories. The time for disintegration of orally disintegrating tablets are generally considered less than one minute. Orally disintegrating tablets are characterized by high porosity, low density and low hardness. When administered, an in-situ suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed[7].

Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. Keeping in view the advantages of this delivery system, in the present study attempts were made to formulate taste masked orally disintegrating tablets of lisinopril which is used in acute diseases like hypertension and heart failure respectively that acts by inhibiting angiotension converting enzyme (ACE)[8]. Taste masking of lisinopril was done by complex formation with betacyclodextrin.

MATERIALS AND METHODS

Materials

Lisinopril was gifted from Dr.Reddy's Laboratories (Hyderabad, India). Crospovidone, Croscarmellose sodium were obtained from SD Fine chem. LTD (Mumbai). Micro crystalline cellulose was purchased from (S.D. Fine Chemicals, Mumbai). Magnesium stearate and talc were obtained from (Loba Chemicals, Mumbai). All other ingredients used were of analytical grade.

Taste masking and Preparation of fast disintegrating tablets of Lisinopril by Kneading technique.[9,10,11]

Required quantity of lisinopril was weighed and sifted through # 40 ASTM SS sieve.Complexation with beta-cyclodextrin was done. Initially, Drug: beta-cyclodextrin ratio was 1:5. Slurry of beta-cyclodextrin was prepared by taking betacyclodextrin: water (5 gm: 5 ml), stirred for 30 minutes. Drug was added, stirred for 2 hours, dried it. Mixed the above powder base with sifted avicel ,crosspovidone, croscaremellose sodium and other exicipients by tumbling.All the ingridients were mixed thoroughly for not less than 5 minutes and untill to get uniform mixed powder. Finally compressed the lubricated powder base on 10 station rotary tabletting machine.

Table 1: Composition of different batches of fast disintegrating Lisinopril tablets

Ingredients	Formulation code					
	F-1	F-2	F-3	F-4	F-5	F-6
Lisinopril	10	10	10	10	10	10
B-Cyclodextrin	50	50	50	50	50	50
Avicel	79	69	59	79	69	59
Lactose	18	18	18	18	18	18
Starch powder	05	05	05	05	05	05
Croscarmellose sodium	30	40	50	-	-	-
Crosspovidone	-	-	-	30	40	50
Sodium saccharin	02	02	02	02	02	02
Vanillin	02	02	02	02	02	02
Magnesium stearate	02	02	02	02	02	02
Talc	02	02	02	02	02	02

Evaluation of granules

The angle of repose was measured by using funnel method[12], which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) [13] were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index [14] of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in Table 2.

Table 2: Data for blend evaluation of formulation (F-1 to F-6)

Parameters	Formulation code					
	F-1	F-2	F-3	F-4	F-5	F-6
Angle of repose	25.59 ± 0.41	28.94 ± 0.23	25.73 ± 0.14	26.45 ± 0.19	26.82 ± 0.79	24.65 ± 0.72
Loose bulk density (LBD) (g/ml)	0.397 ± 0.27	0.562 ± 0.43	0.428 ± 0.49	0.530 ± 0.12	0.451 ± 0.71	0.483 ± 0.49
Tapped bulk density (TBD) (g/ml)	0.563 ± 0.48	0.595 ± 0.48	0.637 ± 0.57	0.692 ± 0.31	0.548 ± 0.19	0.634 ± 0.39
Compressibility index (%)	14.78 ± 0.53	16.81 ± 0.37	14.72 ± 0.87	16.47 ± 0.12	17.41 ± 0.28	15.09 ± 0.15

Evaluation of the tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods [15] shown in Table 3.

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability [16]

Ten tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was measured as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight Variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5% (USP XX).

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 20mg of Lisinopril was dissolved in 100ml of . 0.1N hydrochloric acid, filtered, diluted suitably and analyzed for drug content at 246nm using UV-Visible spectrophotometer (UV 160 Shimadzu, Japan).

Wetting time [17]

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 9ml of buffer solution simulating saliva pH 7.4, which had the following composition, NaCl (0.126g), KCl (0.964g), KSCN (0.189g), KH2PO4 (0.655g) and urea (0.200g) in 1Litre of distilled water. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted. The results are tabulated in Table 3.

Water absorption ratio (R)

The weight of the tablet prior to placement in the petri dish was noted (*wb*) utilizing a Shimadzu digital balance. The wetted tablet was removed and reweighed (*wa*). Water absorption ratio, *R*, was then determined according to the following equation.

$R = 100 \times (w_a - w_b) / w_b$ where *wb* and *wa* were tablet weights before and after water absorption, respectively

In-vitro dispersion time [18]

In-vitro dispersion time was measured by dropping a tablet in a 10ml measuring cylinder containing 6ml of . 0.1N hydrochloric acid

***In vitro* disintegration time**

10 ml of water at 25°C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted.

In-vitro drug release studies

In-vitro drug release studies of all the formulations were carried out using tablet dissolution test apparatus (USP XXII type II Electro lab, Mumbai, India) at 50 rpm. 0.1N hydrochloric acid was used as the dissolution media with temperature maintained at 37±1ºC. Samples were withdrawn at different intervals, diluted suitably and analyzed at 246nm for cumulative drug release using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India). The study was performed in triplicate.

Table 3: **Thickness, hardness, friability, drug content, weight variation, wetting time, water absorption ratio, *in vitro* dispersion time, in vitro disintegration time of Lisinopril fast disintegrating tablets**

Parameters	Formulation code					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Thickness (mm)	2.18 ± 0.14	2.61 ± 0.23	2.45 ± 0.79	2.82 ± 0.15	2.24 ± 0.17	2.10 ± 0.49
Hardness (kg/cm^2)	3.248 ± 1.7	3.351 ± 1.3	3.522 ± 2.5	3.682 ± 2.8	3.731 ± 1.8	3.238 ± 1.4
Friability (%)	0.487	0.541	0.586	0.429	0.561	0.486
Drug content (%)	97.9 ± 0.18	98.3 ± 0.27	99.2 ± 0.18	98.7 ± 0.43	97.1 ± 0.71	99.1 ± 0.08
Weight variation (mg)	201.35	202.14	200.54	199.71	201.59	200.85
Wetting time (sec)	52	48	45	36	31	23
Water absorption ratio	93	98	105	111	125	131
In vitro dispersion time (sec)*	63	55	51	48	45	43
In Vitro disintegrating time (sec)	58	53	49	41	38	32

Stability studies

Short term stability studies on the optimum formulation (F6) were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40°/75% RH for 3 weeks. At every 1 week intervals, the tablets were examined for physical changes, properties, drug content and in vitro release studies [19].

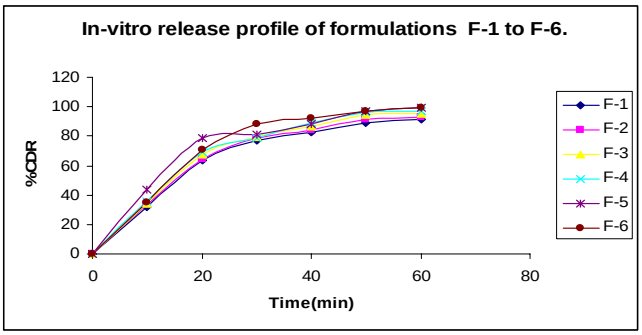

Fig.1: Comparison of *In-vitro* release profile of Lisinopril from formulations F-1 to F-6.

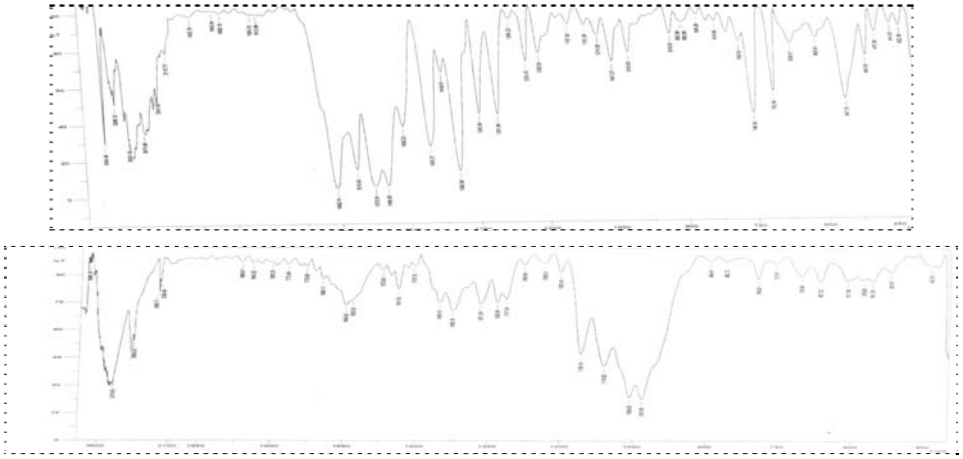

Fig. 2: Fourier transform infrared spectra of A: Pure Lisinopril

B: Lisinopril tablet (From top to bottom)

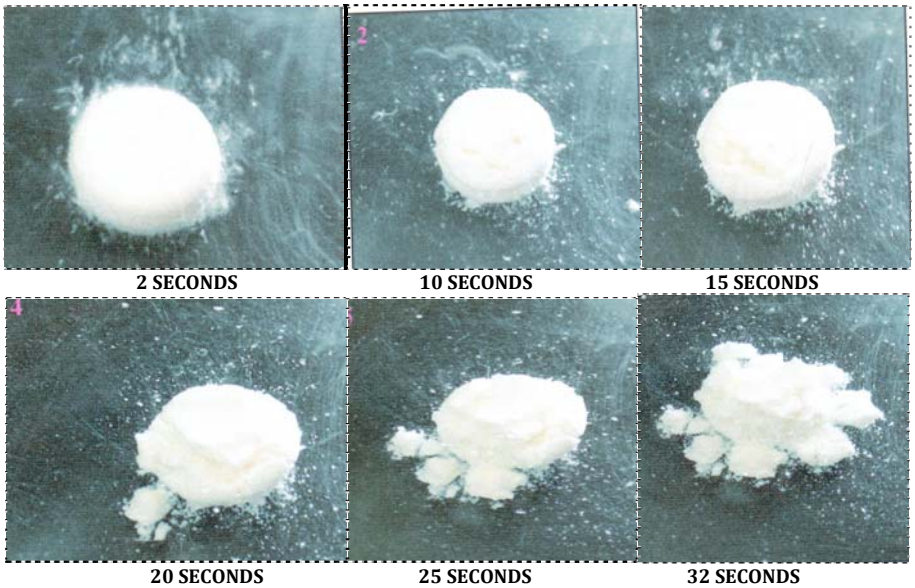

Fig. 2: Process of disintegration of F-6 FDTS

RESULTS AND DISCUSSION

The supplied drug passed the various tests of identification and analysis. The pure drug Lisinopril and the solid admixture of drug and various excipients used in the preparation of fast dispersible tablet formulations were characterized by FT-IR spectroscopy to know the compatability, figure-2. The FT-IR study did not show any possibility of interaction between Lisinopril and superdisintegrants used in the fast dispersible tablets. Since the flow properties of the powder mixture are important for the uniformity of the mass of the tablets, the flow of the powder mixture was analyzed before compression of the tablets. The results of angle of repose and compressibility index (%) ranged from (24.65 ± 0.72 to 28.49 ± 0.23) and (14.72 ± 0.87 to 17.4 ± 0.28), respectively. The results of loose bulk density and tapped bulk density ranged from (0.397 ± 0.27 to 0.562 ± 0.43) and (0.563 ± 0.48 to 0.692 ± 0.31), respectively. The results of angle of repose (<30) indicate good flow properties of granules. This was further supported by lower compressibility index values. The lowest compressibility index is 5-15 % which indicates excellent flow properties (Table 2). The physical properties of different batches of fast dissolving tablets are given in (Table 3). Tablet mean thickness was almost uniform in all the formulations. The thickness varies between 2.10 ± 0.49 to 2.61 ± 0.23 mm. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 3.238 ± 1.4 to 3.731 ± 1.81 kg/sq cm. Friability values below 1% were an indication of good mechanical resistance of the tablets. Formulations prepared by sublimation method were found to be more friable. All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weight variation in all the six formulations was found to be 199.71 to 202.19 mg, which was in pharmacopoeial limits of ±7.5% of the average weight. The percentage drug content of all the tablets was found to be between 97.1 ± 0.71 to 99.2 ± 0.18 % of Lisinopril which was within the acceptable limits. The wetting time for all the six formulations was performed in triplicate. The values lie between 23 to 52 sec. In vitro dispersion is a special parameter in which the time taken by the tablet to produce complete dispersion is measured. The time for all the six formulations varied between 43 to 63 sec. Tablets were prepared with croscarmellose sodium F-1 to F-3 and with crospovidone F-4 to F-6. The wetting time, in vitro dispersion time of the tablets were also considerably reduced in tablets containing crospovidone which may be attributed due to the wicking type of disintegrants (crospovidone) formed thus facilitating the disintegrants to bring about faster disintegration. The results of water absorption ratio (%) and in vitro disintegrating time (sec) ranged from (93 to 131) and (32 to 58), respectively.

The *in vitro* dissolution profile indicated faster and maximum drug release from formulation F6. Stability studies shown that there was no significant change when compared with zero day of formulation (F-6). The disintegration time of crospovidone tablets are comparatively lower than the sodium starch glycolate. The faster disintegration of crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus, these results suggest that the disintegration time can be decreased by using wicking type of disintegrants (crospovidone).

CONCLUSION

The oral disintegrating tablets of Lisinopril with sufficient mechanical strength, acceptable taste and smaller disintegration time were achieved employing suitable superdisintegrants and other excipients at optimum concentration. Stability studies revealed that there was no significant change in drug content and dissolution profile of oral disintegrating tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Lisinopril and other ingredients used. Among two superdisintegrants used cross povidone showed better performance in disintegration time when compared to croscaremellose sodium. In the *in vitro* dissolution study of F-6 shows 35.25% release of drug with in two minutes and 99.46% with in 60 minutes So the formulation of F6 was found to be best among all other formulations, because it has exhibited faster wetting time, good taste and faster disintegration time when compared to all other formulations.

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